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(54) Title: <b>ANTICONVULSANT SULFAMATE DERIVATIVES USEFUL IN TREATING OBESITY</b>			
(57) Abstract <p>Anticonvulsant derivatives useful in treating obesity are disclosed.</p>			

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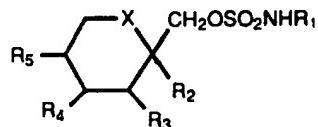
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## ANTICONVULSANT SULFAMATE DERIVATIVES USEFUL IN TREATING OBESITY

## BACKGROUND OF THE INVENTION

5

## Compounds of Formula I:



- 10 are structurally novel antiepileptic compounds that are highly effective anticonvulsants in animal tests (Maryanoff, B.E., Nortey, S.O., Gardocki, J.F., Shank, R.P. and Dodgson, S.P. *J. Med. Chem.* 30, 880-887, 1987; Maryanoff, B.E., Costanzo, M.J., Shank, R.P., Schupsky, J.J., Ortegon, M.E., and Vaught J.L. *Bioorganic & Medicinal Chemistry Letters* 3, 2653-2656, 1993, McComsey, D. F. and Maryanoff B. E., *J. Org.* 59, 2652 *Chem.* 1995). These compounds are covered by US Patent No. 4,513,006. One of these compounds 2,3:4,5-bis-O-(1-methylethyldene)- $\beta$ -D-fructopyranose sulfamate known as topiramate has been demonstrated in clinical trials of human epilepsy to be effective as adjunctive therapy or as monotherapy in treating simple and complex partial seizures and secondarily generalized seizures (E. FAUGHT, B.J. WILDER, R.E. RAMSEY, R.A. REIFE, L.D. KRAMER, G.W. PLEDGER, R.M. KARIM et. al., *Epilepsia* 36 (S4) 33, 1995; S.K. SACHDEO, R.C. SACHDEO, R.A. REIFE, P. LIM and G. PLEDGER, *Epilepsia* 36 (S4) 33, 1995), and is currently marketed for the treatment of simple and complex partial seizure epilepsy with or without secondary generalized seizures in Great Britain, Finland, the United States and Sweden and applications for regulatory approval are presently pending in numerous countries throughout the world.
- 20
- 25

- Compounds of Formula I were initially found to possess anticonvulsant activity in the traditional maximal electroshock seizure (MES) test in mice
- 30

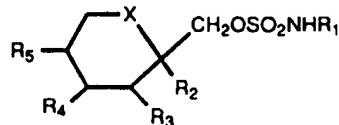
(SHANK, R.P., GARDOCKI, J.F., VAUGHT, J.L., DAVIS, C.B., SCHUPSKY, J.J., RAFFA, R.B., DODGSON, S.J., NORTEY, S.O., and MARYANOFF, B.E., Epilepsia 35 450-460, 1994). Subsequent studies revealed that Compounds of Formula I were also highly effective in the MES test in rats. More recently 5 topiramate was found to effectively block seizures in several rodent models of epilepsy (J. NAKAMURA, S. TAMURA, T. KANDA, A. ISHII, K. ISHIHARA, T. SERIKAWA, J. YAMADA, and M. SASA, Eur. J. Pharmacol. 254 83-89, 1994), and in an animal model of kindled epilepsy (A. WAUQUIER and S. ZHOU, Epilepsy Res. 24, 73-77, 1996).

10

Recent preclinical studies on topiramate have revealed previously unrecognized pharmacological properties which suggest that topiramate should be effective in treating obesity.

## 15 DISCLOSURE OF THE INVENTION

Accordingly, it has been found that compounds of the following formula I:

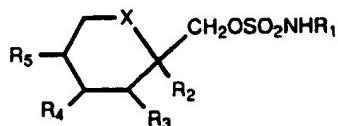


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wherein X is O or CH<sub>2</sub>, and R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, R<sub>4</sub> and R<sub>5</sub> are as defined hereinafter are useful in treating obesity.

## 25 DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

The sulfamates of the invention are of the following formula (I):



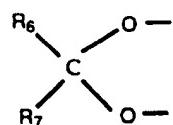
wherein

5        X is CH<sub>2</sub> or oxygen;

R<sub>1</sub> is hydrogen or alkyl; and

R<sub>2</sub>, R<sub>3</sub>, R<sub>4</sub> and R<sub>5</sub> are independently hydrogen or lower alkoxy, when X is oxygen, R<sub>2</sub> and R<sub>3</sub> and/or R<sub>4</sub> and R<sub>5</sub> together may be a methylenedioxy group of the following formula (II):

10



wherein

R<sub>6</sub> and R<sub>7</sub> are the same or different and are hydrogen, lower alkyl or are

15        alkyl and are joined to form a cyclopentyl or cyclohexyl ring.

R<sub>1</sub> in particular is hydrogen or alkyl of about 1 to 4 carbons, such as methyl, ethyl and iso-propyl. Alkyl throughout this specification includes straight and branched chain alkyl. Alkyl groups for R<sub>2</sub>, R<sub>3</sub>, R<sub>4</sub>, R<sub>5</sub>, R<sub>6</sub> and R<sub>7</sub> are of about 1 to 3 carbons and include methyl, ethyl, iso-propyl and n-propyl.

20

A particular group of compounds of formula (I) are those wherein X is oxygen and both R<sub>2</sub> and R<sub>3</sub>, and R<sub>4</sub> and R<sub>5</sub> together are methylenedioxy groups of the formula (II), wherein R<sub>6</sub> and R<sub>7</sub> are both hydrogen, both alkyl, or combine to form a spiro cyclopentyl or cyclohexyl ring, in particular where R<sub>6</sub>

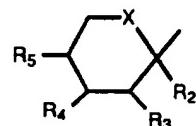
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and R<sub>7</sub> are both alkyl such as methyl. A second group of compounds are those wherein X is CH<sub>2</sub> and R<sub>4</sub> and R<sub>5</sub> are joined to form a benzene ring. A third

group of compounds of formula (I) are those wherein both R<sub>2</sub> and R<sub>3</sub> are hydrogen.

The compounds of formula (I) may be synthesized by the following  
5 methods:

- (a) Reaction of an alcohol of the formula RCH<sub>2</sub>OH with a chlorosulfamate of the formula CISO<sub>2</sub>NH<sub>2</sub> or CISO<sub>2</sub>NHR<sub>1</sub> in the presence of a base such as potassium a-butoxide or sodium hydride at a temperature of about  
10 -20° to 25° C and in a solvent such as toluene, THF or dimethylformamide wherein R is a moiety of the following formula (III):



- 15 (b) Reaction of an alcohol of the formula RCH<sub>2</sub>OH with sulfonylchloride of the formula SO<sub>2</sub>Cl<sub>2</sub> in the presence of a base such as triethylamine or pyridine at a temperature of about -40° to 25° C in a solvent such as diethyl ether or methylene chloride to produce a chlorosulfate of the formula RCH<sub>2</sub>OSO<sub>2</sub>Cl.

- 20 The chlorosulfate of the formula RCH<sub>2</sub>OSO<sub>2</sub>Cl may then be reacted with an amine of the formula R<sub>1</sub>NH<sub>2</sub> at a temperature of about 40° to 25° C in a solvent such as methylene chloride or acetonitrile to produce a compound of formula (I). The reaction conditions for (b) are also described by T. Tsuchiya et  
25 al. in Tet. Letters, No. 36, p. 3365 to 3368 (1978).

- (c) Reaction of the chlorosulfate RCH<sub>2</sub>OSO<sub>2</sub>Cl with a metal azide such as sodium azide in a solvent such as methylene chloride or acetonitrile yields an azidosulfate of the formula RCH<sub>2</sub>OSO<sub>2</sub>N<sub>3</sub> as described by M.

Hedayatullah in Tet. Lett. p. 2455-2458 (1975). The azidosulfate is then reduced to a compound of formula (I) wherein R<sub>1</sub> is hydrogen by catalytic hydrogenation, e.g. with a noble metal and H<sub>2</sub> or by heating with copper metal in a solvent such as methanol.

5

The starting materials of the formula RCH<sub>2</sub>OH may be obtained commercially or as known in the art. For example, starting materials of the formula RCH<sub>2</sub>OH wherein both R<sub>2</sub> and R<sub>3</sub>, and R<sub>4</sub> and R<sub>5</sub> are identical and are of the formula (II) may be obtained by the method of R. F. Brady in Carbohydrate

- 10 Research, Vol. 14, p. 35 to 40 (1970) or by reaction of the trimethylsilyl enol ether of a R<sub>6</sub>COR<sub>7</sub> ketone or aldehyde with fructose at a temperature of about 25° C, in a solvent such a halocarbon, e.g. methylene chloride in the presence of a protic acid such as hydrochloric acid or a Lewis Acid such as zinc chloride. The trimethylsilyl enol ether reaction is described by G. L. Larson et al in J. Org. 15 Chem. Vol. 38, No. 22, p. 3935 (1973).

Further, carboxylic acids and aldehydes of the formulae RCOOH and RCHO may be reduced to compounds of the formula RCH<sub>2</sub>OH by standard reduction techniques, e.g. reaction with lithium aluminum hydride, sodium

- 20 borohydride or borane-THF complex in an inert solvent such a diglyme, THF or toluene at a temperature of about 0° to 100° C, e.g. as described by H.O. House in "Modern Synthetic Reactions", 2nd Ed., pages 45 to 144 (1972).

- 25 The compounds of formula I: may also be made by the process disclosed US Patent: No.4,513,006, which is incorporated by reference herein.

The compounds of formula I include the various individual isomers as well as the racemates thereof, e.g., the various alpha and beta attachments, i.e., below and above the plane of the drawing, of R<sub>2</sub>, R<sub>3</sub>, R<sub>4</sub> and R<sub>5</sub> on the 6-

- 30 membered ring. Preferably, the oxygens of the methylenedioxy group (II) are attached on the same side of the 6-membered ring.

The activity of the compounds of formula I in treating obesity was first evidenced in several preclinical long term (three months to two years) studies.

Topiramate caused a significant reduction in the rate of weight gain, or a weight

5 loss in rodents and dogs at doses as low as 10 mg/kg p.o. Analysis of food consumption in these studies indicated that the effect of topiramate on body weight was due primarily to a decrease in metabolic efficiency rather than a decrease in food consumption. In clinical studies in which topiramate was administered to patients with epilepsy, a loss of body weight was a statistically

10 significant side-effect.

For treating obesity, a compound of formula (I) may be employed at a daily dosage in the range of about 50 to 200 mg, usually in two divided doses, for an average adult human. A unit dose would contain about 25 to 100 mg of the

15 active ingredient.

To prepare the pharmaceutical compositions of this invention, one or more sulfamate compounds of formula (I) are intimately admixed with a pharmaceutical carrier according to conventional pharmaceutical compounding

20 techniques, which carrier may take a wide variety of forms depending on the form of preparation desired for administration, e.g., oral, by suppository, or parenteral. In preparing the compositions in oral dosage form, any of the usual pharmaceutical media may be employed. Thus, for liquid oral preparations, such as for example, suspensions, elixirs and solutions, suitable carriers and

25 additives include water, glycols, oils, alcohols, flavoring agents, preservatives, coloring agents and the like; for solid oral preparations such as, for example, powders, capsules and tablets, suitable carriers and additives include starches, sugars, diluents, granulating agents, lubricants, binders, disintegrating agents and the like. Because of their ease in administration, tablets and capsules

30 represent the most advantageous oral dosage unit form, in which case solid pharmaceutical carriers are obviously employed. If desired, tablets may be sugar coated or enteric coated by standard techniques. Suppositories may be

prepared, in which case cocoa butter could be used as the carrier. For parenterals, the carrier will usually comprise sterile water, though other ingredients, for example, for purposes such as aiding solubility or for preservation, may be included. Injectable suspensions may also be prepared

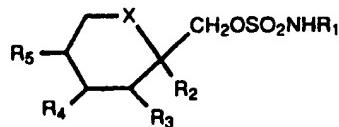
- 5 in which case appropriate liquid carriers, suspending agents and the like may be employed. Topiramate is currently available for oral administration in round tablets containing 25 mg, 100 mg or 200 mg of active agent. The tablets contain the following inactive ingredients: lactose hydrous, pregelatinized starch, microcrystalline cellulose, sodium starch glycolate, magnesium stearate,
- 10 purified water, carnauba wax, hydroxypropyl methylcellulose, titanium dioxide, polyethylene glycol, synthetic iron oxide, and polysorbate 80.

The pharmaceutical compositions herein will contain, per dosage unit, e.g., tablet, capsule, powder injection, teaspoonful, suppository and the like

- 15 from about 25 to about 200 mg of the active ingredient.

**WHAT IS CLAIMED IS:**

1. A method for treating obesity comprising administering to a mammal afflicted  
 5 with such condition a therapeutically effective amount for treating such condition  
 of a compound of the formula I:

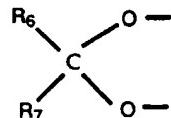


10 wherein

X is CH<sub>2</sub> or oxygen;

R<sub>1</sub> is hydrogen or alkyl; and

- R<sub>2</sub>, R<sub>3</sub>, R<sub>4</sub> and R<sub>5</sub> are independently hydrogen or lower alkyl and, when  
 15 X is oxygen, R<sub>2</sub> and R<sub>3</sub> and/or R<sub>4</sub> and R<sub>5</sub> together may be a methylenedioxy  
 group of the following formula (II):



20 wherein

R<sub>6</sub> and R<sub>7</sub> are the same or different and are hydrogen, lower alkyl or are  
 alkyl and are joined to form a cyclopentyl or cyclohexyl ring.

2. The method of claim 1 wherein the compound of formula I is topiramate.

25

3. The method of claim 1, wherein the therapeutically effective amount is of  
 from about 50 to 400 mg.

4. The method of claim 1, wherein the amount is of from about 25 to 200 mg.